IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Klaus Sommermeyer

Application No.: 10/537,176 Group: 1623

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Confirmation No.: 8000

For: ALDONIC ACID ESTERS, METHODS FOR PRODUCING THE SAME, AND METHODS FOR PRODUCING PHARMACEUTICAL ACTIVE INGREDIENTS COUPLED TO POLYSACCHARIDES OR POLYSACCHARIDE DERIVATIVES ON FREE AMINO GROUPS

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REPLY TO RESTRICTION REQUIREMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Responsive to the Restriction Requirement dated June 26, 2008, the claims of Group I (Claims 35-53 and 68) drawn to an aldonic acid ester of polysaccharides or polysaccharide derivatives are elected, with traverse, for prosecution. Applicant reserves the right to file a continuing application or take such other appropriate action as deemed necessary to protect the non-elected inventions. Applicant does not hereby abandon or waive any rights in the non-elected inventions.

Responsive to the requirement for an election of species for searching purposes, Applicant hereby elects the compound of Example 5, HES 50/0.7 as the species. Claims readable on the elected species are 35-53 and 68.

The requirement is being traversed for the reasons set forth in detail below.

Applicants Traverse Restriction Requirement

The Examiner stated that the inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because they lack the same or corresponding special technical feature under PCT Rule 13.2. The Examiner stated that the common technical feature for the Groups I and II is an aldonic ester of a polysaccharide and that this element can not be a special technical feature under PCT Rule 13.2 because it lacks novelty over PCT Publication WO 2002/080979 by Sommermeyer *et al.*, or the corresponding US Publication Number 2005/0063943 (hereinafter, the "'943 publication").

Specifically, the Examiner alleges that the '943 publication teaches hydroxyalkyl starch covalently bonded to an active ingredient either directly or indirectly via a linker. For conjugation to the linker, hydroxyalkyl starch is first oxidized at the reducing end sugar unit (paragraph 0031) and that suitable linkers include oxylamine derivatives (paragraphs 0125 and 0126). Furthermore, the Examiner is concluding that "conjugation of hydroxyalkyl starch, oxidized at the reducing end, with an oxylamine derivative results in the formation of an ester on the reducing end of the hydroxyalkyl starch" and that "this product is also known as an aldonic acid ester of a polysaccharide".

Applicants respectfully disagree with these conclusions.

For the reasons provided below, paragraphs 0031, 0125 and 0126 of the '943 publication do not disclose an aldonic ester of a polysaccharide. Paragraph 0125 of the '943 publication describes oxyamine derivatives as linkers, but not aldonic esters of a polysaccharides. Paragraph 0125 of the '943 publication also cites two additional references in connection to use of oxylamine derivatives as linkers: WO97/38727 (hereinafter, the "'727 publication") and EP 605 963 (hereinafter, the "'963 publication"). Applicants note that the '727 publication <u>does not</u> teach an aldonic <u>ester</u> of a polysaccharide. The '727 publication discloses coupling of saccharides having a carboxyl group with a spacer through the amide linkage and the spacer coupling to a medicament via an ester linkage (Abstract of the '727 publication):

"A composite of medicaments each having a hydroxyl group and represented by the following general formula: A-B-C, wherein A represents a carrier selected among saccharides each having a carboxyl group, polyethylene glycol, aliphatic carboxylic acids and their derivatives, B represents a spacer having amino and carboxyl groups in its molecule, and C represents a medicament having a hydroxyl group. In this case, the carrier A and the spacer B are bonded to each other through the amide linkage formed between the carboxyl group of the carrier A and the amino group of the spacer B, while the spacer B and the medicament C are bonded to each other through the ester bond formed between the carboxyl group of the spacer B and the hydroxyl group of the medicament C. The composite exhibits a surely controlled release rate of the medicament therefrom to increase the migration of the medicament to a target tissue and/or to enhance the efficacy of the medicament." (Abstract)

There is no teaching of an aldonic ester of a polysaccharide. The '963 publication discloses oxylamine derivatives (page 7, lines 43-53):

(XIX) P-O-CH_2CH_2-CO-ONH_2;
(XX) P-O-CH_2CH_2-O-CO-ONH_2;
(XXI) P-O-CH_2CH_2-NH-CO-ONH_2;
(XXII) P-O-CH_2CH_2-NH-CS-ONH_2;
(XXIII) P-O-CH_2CH_2-ONH_2;
(XXIV) P-O-CH_2CH_2-NH-CO-CH_2ONH_2;
(XXV) P-O-CH_2CH_2-O-CO-CH_2-ONH_2;
(XXVI) P-O-CH_2CH_2-CH(OH)-CH_2-ONH_2; and
(XXVII) P-O-CH_2CH_2-CO-CH_2-ONH_2.

and oxylamine-modified polypeptides(page 9, 1-11):

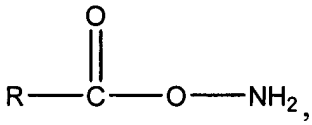
(XXVIII) [P-O-CH_2CH_2-CO-ON=CH-]$_n$-Z;
(XXIX) [P-O-CH_2CH_2-O-CO-ON=CH-]$_n$-Z;
(XXX) [P-O-CH_2CH_2-NH-CO-ON=CH-]$_n$-Z;
(XXXI) [P-O-CH_2CH_2-NH-CS-ON=CH-]$_n$-Z;
(XXXII) [P-O-CH_2CH_2-ON=CH-]$_n$-Z;
(XXXIII) [P-O-CH_2CH_2-NH-CO-CH_2-ON=CH-]$_n$-Z;
(XXXIV) [P-O-CH_2CH_2-O-CO-CH_2-ON=CH-]$_n$-Z;
(XXXV) [P-O-CH_2CH_2-CH(OH)-CH_2-ON=CH-]$_n$-Z; and
(XXXVI) [P-O-CH_2CH_2-CO-CH_2-ON=CH-]$_n$-Z.

As can be seen from the above, the oxylamine derivatives as mentioned in the '963 publication are not esters.

Furthermore, the reaction of an oxylamine with a carboxylic acid would, in the first instance, require an activation agent for the carboxylic acid, and in the second instance, would

result in a hydroxamic acid and not an ester. The support for this assertion is submitted herein as an Exhibit A. The Exhibit A is a copy of pages 370-371, from "Advanced Organic Chemistry", Jerry March, publisher John Wiley and Sons, New York, Chichester, Brisbane, Toronto, Singapure. The Examiner is referred to Section 0-54 on page 370, showing that a carboxylic acid is commonly converted to a more reactive acid halide before reacting with an amine to form an amide. It is well known to one skilled in the art of chemistry that if oxylamine is used instead of an amine, a hydroxamic acid would be formed. To further support the assertion that the reaction of an oxylamine with a carboxcylic acid produces hydroxamic acid and not an ester, Exhibit B is submitted herein. Exhibit B is a copy of page 193, from "Methoden der organischen Chemic", Houben-Weyl, publisher George Thieme Verlag, Stuttgart. The Examiner is referred to the first reaction showing the formation of hydroxamic acid in the reaction of carboxylic acid derivatives and hydroxylamine. This is also shown in the second full paragraph in Section 0-54 in Exhibit A.

Even if hydroxylamine would react with an activated carboxylic acid at the hydroxyl group instead of at the amine, a compound of the following structure would form:



, which is not an ester. A definition of an ester is provided in Exhibit C, which is enclosed herein. Exhibit C is a printout from an online dictionary of Organic Compounds: http://www.ben.mills.btinternet.co.uk/chemistry/dict.htm, (last time accessed on September 25, 2008). For the definition of an ester, the Examiner's attention is drawn to the page 3 of Exhibit C (highlighted), which states that an ester is "[a] molecule made from an alcohol and a carboxylic acid."

In the view of the above, Applicants conclude that the '943 publication does not disclose an aldonic ester of a polysaccharide. Under PCT Rules 13.1 and 13.2, in order to assert lack of unity, the Examiner should present evidence that the special technical feature is not novel. Since such evidence is absent, the restriction requirement is improper and Applicants respectfully request that restriction requirement be withdrawn.

An extension of time to respond to the Restriction Requirement is respectfully requested. A Petition for an Extension of Time and the appropriate fee are being filed concurrently.

Respectfully submitted,

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By _____

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